1 **Recruitment barriers for prophylactic vaccine trials: a study in Belgium**

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Abstract

Recruitment of volunteers is one of the main challenges in clinical trial management, and there is little information about recruitment barriers for preventative vaccine trials. We investigated both the recruitment barriers and recruitment strategies for preventive vaccine trials in Belgium. A 10 minute survey was used as well as interviews of staff at all clinical trial sites in Belgium that regularly perform vaccine trials. We observed that there are successful recruitment strategies and few recruitment issues for trials involving healthy adults and those over 65 years old. However, challenges face the recruitment of paediatric populations, pregnant women, patients and the very elderly (over 85 years old). From these results, we identified three priority areas to increase recruitment for prophylactic vaccine trials in Belgium. These are: the lack of public knowledge about infectious diseases; the lack of resources of healthcare professionals to take part in clinical trials; and the burden to potential volunteers to take part in a trial. These were discussed with stakeholders and solutions were proposed.

Introduction

Clinical trials are crucial for the progress of medicine. They test whether an intervention – for example a new drug, vaccine or diagnostic tool – is safe and works for its targeted use in man. The number of subjects needed to prove this is carefully calculated, however, reaching this recruitment target is one of the greatest challenges in clinical trial management (1). The validity of the study results can therefore be affected by missed recruitment targets. Poor recruitment causes costly delays and even early termination of trials, which slows down drug development. A study in the UK showed that approximately half of clinical trials achieve their recruitment target, and approximately one third of trial terminations occur during the recruitment stage (1). Frequent barriers for volunteering include travel time and inconvenient visit schedules (2-6). The selection criteria, the

protocol, training in recruitment, resources and experience of the research team also affect recruitment (1-5, 7-9).

Belgium is an important country for clinical trials. It has the second highest clinical trial site density in the world (10, 11) and approximately 1500 sponsor-driven and academic trials running throughout the year (12). Belgium is a key country in vaccinology with the presence of major companies and several small and medium sized Belgian enterprises active in the vaccine field. There is also a strong academic presence in vaccinology, and the Belgian Federal Agency for Medicines and Health Products has a dedicated vaccines spearhead. In 2010, 6.5% of newly started clinical trials in Belgium were to test a preventative or therapeutic vaccine (11).

There is a large body of literature about recruitment barriers but little is specific to prophylactic vaccine trials (PVT). Unlike patient studies, PVT typically involve subjects who have never had the disease targeted by the candidate PV. Furthermore, the motivations to volunteer can be very different. These include altruism and personal benefit (for example health benefits or financial compensation, 5, 13, 14, 15). It is important to gain more insight into PVT recruitment barriers in order to facilitate the development of innovative vaccines that will improve public health. Some studies observed that the travel distance to the trial site, age, and safety concerns affect study recruitment or enrolment (for a review, see 16). However, to our knowledge, no studies have assessed the broader aspects of recruitment barriers for PVT, from the perspectives of researchers and healthcare professionals. The present study addresses this knowledge gap by assessing recruitment barriers for PVT in Belgium.

Methods

Survey

The survey was built using an online tool (SurveyMonkey Inc, CA, USA). It was tested and validated for functionality on different devices (desktop, tablet and smartphone) and for time to complete (<10

minutes). The survey was sent by email to individuals involved in a PVT in Belgium between 2011 and 2015, and Belgian clinical research associations. Survey invitees (>100 people) were allowed to send the survey link onto their community. As a result, we cannot measure the response rate.

The survey was open between the 17th of November and the 18th of December 2016. Respondents were asked multiple choice questions about: their professional background; their experience in recruiting different subject populations; the impact and frequency of different recruitment barriers; and the success of various recruitment strategies. Subject populations were identified from clinical trial applications submitted to the National Regulatory Authority, 2011–2015. Recruitment barriers and strategies were identified from a literature review, not all specific to PVT (Supplementary Tables 1 and 2). Respondents could leave a comment after each question so that we could gather information not captured in the multiple choices. Responses were submitted anonymously. Results are presented as the percentage of participants reporting each response (one decimal place). Comments were analysed qualitatively.

Interviews

From January to March 2017, we interviewed researchers at the four major sites where PVT are regularly performed in Belgium: the Center for Vaccinology (CEVAC), Ghent University Hospital; Leuven University Vaccinology Center, KU Leuven; SGS, Antwerp; and Centre for the Evaluation of Vaccination, University of Antwerp. We also interviewed a former investigator from ImmuneHealth, Charleroi, who ran PVT in the past. The aims of the interviews were to gain detailed perspectives on recruitment and identify potential future strategies to improve recruitment. Responses were analysed qualitatively.

The survey and interview questions are found in the Supplementary Information.

Results

Survey respondent demographics

We received 34 responses to our survey. Nine were excluded because no questions about recruitment were answered. Retained respondents came from the private sector (CRO, n=7; investigator site, n=2; sponsor organisation, n=5) and a public investigator site, n=8 (Supplementary Figure 1). Three respondents reported that they came from an “other” organisation: a “university/ethics committee”; a “hospital with a clinical research centre”; and a “public investigator and sponsor site”. Most respondents are involved in 1–3 PVT per year (52%). The rest are involved in 4–6 (36%) or more than 10 (12%) PVT per year (Supplementary Figure 2).

Respondents’ experience in trials with different subject populations was inferred from survey responses (see Supplementary Information). Most respondents have experience in trials that recruit healthy adults (88%), the elderly over 65 years old (76%) and/or patients (72%). Respondents had least experience in paediatric trials (infants, 52%; and adolescents, 48%) and trials involving pregnant women (36%, Supplementary Figure 3).

Survey results about recruitment targets

Recruitment is most successful for healthy adults and the elderly (65+ years old; 69.6% and 43.5% “never miss” target, respectively; 0% often/always miss, Figure 1). Combining the “often” and “always” miss scores, the most difficult to recruit are: the very elderly (85+, 50%); infants and children (13.6%); adolescents (4.5%); and patients (4.5%). Of those that have experience recruiting pregnant women (37.5%), more reported that they “sometimes miss” their recruitment targets (29.2% of total responses).

The most common topics in the comments (n=17) were about difficulties recruiting young children (n= 7) and the very elderly (n= 4). Other comments mentioned difficulties recruiting healthy volunteers (n=2) and specific patient populations (n=2). Two respondents reported that: it’s difficult to find volunteers that haven’t already been vaccinated with a certain vaccine (e.g. hepatitis B vaccine); vaccination in Belgium is relatively complete, which alludes to the previous point; and the

protocol is sometimes not aligned with Belgium's vaccination schedule for infants, which is a barrier for comparator studies.

Survey results about recruitment barriers

The barriers most rated as having a "big effect" on recruitment are: the selection criteria (60.9%); the visit schedule (59.1%); human resources (HR) dedicated to recruitment (50%); and public knowledge of the disease (50%, Figure 2). Survey respondents reported that the most frequent barrier is the public's knowledge of the disease targeted by the candidate vaccine (Figure 3). 45% of respondents reported that this "often" has an effect. Other factors most rated as "often" affecting recruitment are: the recruitment budget (40%); training/experience in recruitment (35%); and HR dedicated to recruitment (35%). The selection criteria are also a frequent barrier (40% "often", 40% "sometimes"). The highest impact and highest frequency barrier is therefore public knowledge about the disease targeted by the candidate vaccine.

Barriers most often reported to have "some effect" on recruitment are: other protocol-related issues (72.7%); vaccine hesitancy (76.2%); trial design (68.2%); access to the trial site (54.5%); the recruitment budget (54.5%); public knowledge about clinical trials (40.9%); and training/experience in recruitment (40.9%). Barriers mostly rated as "sometimes" having an effect on recruitment are: other protocol-related issues (65%); vaccine hesitancy (55%); the visit schedule (45%); the trial design (45%); public knowledge about clinical trials (35%); and transport access to the trial site (33.3%).

The barriers that most respondents rated as having "no effect" on recruitment are: the consent process (50%); and disincentives of healthcare professionals (HCPs) to recruit (36.4%).

According to survey comments (n=10), recruitment barriers vary according to the subject population.

The trial design (n=1), number of blood draws (n=2) and parental consent requirements (n=1) are barriers for the recruitment of paediatric populations; access to the trial site (n=1) and the length of the informed consent form (n=1) affect recruitment of the elderly; the visit schedule is a barrier for

138 the recruitment of adults (n=1); and recruitment of non-healthy volunteers is difficult for trials of PVs
139 against low burden diseases (n=1). Subject remuneration was raised as a barrier in three of the
140 comments.

141 **Interview results about recruitment barriers**

142 Interviewees agreed with the population-dependent recruitment rates reported in the survey, and
143 generally agreed with the survey results on recruitment barriers. Additional comments are described
144 below.

145 All of the clinical trial sites have collaborated with other HCPs (mainly physicians, outside of the trial
146 centre) to access patients, pregnant women, children and sometimes elderly populations. An
147 additional barrier raised by four of the sites is the lack of time and resources of these HCPs, despite
148 enthusiasm towards PVT, and some reported insufficient training in vaccinology and clinical trials of
149 HCPs. This hinders collaboration necessary for recruitment of these populations.

150 Unanimously, interviewees reported that the main motivation of their volunteers is either personal
151 (potential protection against a disease) or altruistic (contributing to medicine) and that subject
152 remuneration, despite being lower than some drug trials, is therefore not a barrier. This is in contrast
153 to the survey comments. Nevertheless, all interviewees agreed that reducing the subject fee under a
154 critical minimum would negatively affect recruitment. The consent process was raised by only one
155 interviewee as a recruitment barrier.

156 Interviewees agreed with the subject-specific recruitment barriers raised in the survey comments.
157 The selection criteria was not raised as an over-arching or systematic barrier for PVT, but was raised
158 as an issue for elderly subjects because of the health heterogeneity of this population. The visit
159 schedule was raised by two sites as a barrier for active populations. The (very) elderly's reduced
160 mobility due to illness or lack of transport was highlighted by four of the sites as a significant barrier.

The site with experience in recruiting pregnant women reported that the short time-frame and labour-intensive recruitment are barriers for recruiting pregnant women.

Survey results about recruitment strategies

Overall, all strategies listed improve recruitment, since more survey respondents reported that the strategies listed work, than don't work (Figure 4). The most popular and effective strategies are: having dedicated staff for recruitment (85.7% reported that this works, 4.8% disagreed); having a database of eligible volunteers (81% reported that this works, 0% disagreed); advertising via social media (66.7% reported that this works, 9.5% disagreed); and adapting the selection criteria (57.1% reported that this works, 4.8% disagreed). The strategies most often reported as not working are advertising in public spaces (19%) and the sponsor helping the investigator (23.8%). The strategies least used by survey respondents are investigator electronic reminder systems and simplifying the consent process (42.9% and 42.8% have experience, respectively). Some respondents have no intention to adapt the protocol (19.1%) or simplify the consent process (14.3%). The strategy that most respondents plan to try is public awareness sessions (19%). This is promising, since one of the biggest barriers identified in this study is public awareness about diseases targeted by candidate vaccines.

Two main themes emerged from the comments about recruitment strategies (n=10): increased remuneration for volunteers (n=3); and awareness campaigns on the importance of PVT to the public and HCPs (n=5). Other recommendations were: shorter study durations; advertising in general practitioners' practices; and word-of-mouth. One respondent raised the importance of staff structure at investigator sites and staff stability in hospital settings. Two comments elsewhere in the survey mentioned that collaboration with paediatricians or well-baby clinics could improve recruitment of young children.

Interview results about recruitment strategies

185 Interviewees generally agreed with the reported effectiveness of recruitment strategies. Below are
186 additional comments.

187 All trial sites use a database as their primary source of subjects for trials requiring healthy adults and
188 elderly people, and have dedicated HR for recruitment. To replenish their databases or recruit other
189 subject populations, all sites use mainstream advertising and some recently adopted social media
190 advertising, when authorised by ethics committees. The latter was reported to be particularly
191 effective for the elderly, along with advertising via social clubs. Advertising in newspapers was
192 reported by two teams as inefficient and costly. More effective strategies include: distributing flyers
193 at student fairs; advertising in community magazines; and word-of-mouth. Two of the clinical trial
194 sites adapt their opening hours, therefore mitigating the barrier of inconvenient visit schedules.

195 Three trial site teams reported that recruiting infants was easier in the past thanks to a network of
196 paediatricians in Belgium and their involvement with well-baby clinics. All interviewees agreed that
197 renewed paediatric networks would facilitate recruitment of paediatric populations. Some
198 questioned the feasibility of collaborating with the well-baby clinics today. Two trial site teams
199 suggested increasing the mobility of the conduct of clinical trials to increase recruitment, based on
200 their experience of performing PVT in schools in the past.

201 Interviewees did not agree that increasing subject remuneration or adapting the selection criteria are
202 feasible or effective strategies.

203 **Discussion**

204 Recruitment is still a challenge in clinical trial management. Understanding the recruitment barriers
205 for PVT is therefore important to help researchers achieve their recruitment targets. Our survey and
206 interviews showed that recruitment targets are often met for PVT involving healthy adults and the
207 elderly (65+ years old) in Belgium. We can interpret this in several ways: that these groups are
208 accessible and motivated therefore easy to recruit; that the recruitment targets set are appropriate

to the recruitment environment; that the recruitment strategies are well adapted to the target population; or a combination of these. The present study shows that recruitment strategies are suited to the target population and are adapted over time (e.g. adopting social media). Nevertheless, there are challenges in recruiting patients, pregnant women, paediatric populations and the very elderly (85+ years old).

According to study participants, the biggest barriers for PVT in Belgium are: the lack of public awareness about infectious diseases; the lack of resources for HCPs outside of a full-time research setting to recruit; and the burden to potential volunteers to take part in a PVT. The first is an important barrier because the overarching motivator to volunteer for PVT is personal benefit or altruism, both of which are sensitive to disease awareness and appreciation of PV development. Vaccine hesitancy might have some role, although it's important to note that vaccine confidence in Belgium fairs reasonably well for Europe (17). The second point affects the recruitment of patients, pregnant women, paediatric populations and the very elderly, since collaboration with HCPs is often required to access these populations. Addressing this challenge, which has also been identified by numerous other studies (1-5, 7, 18, 19), would potentially have the biggest positive impact on PVT recruitment in Belgium. Finally, the burden to participate in a PVT encompasses many barriers and for different subject populations, from the visit schedule for active populations and mobility issues for the very elderly. This increased effort to participate might outweigh the person's motivation to volunteer for a PVT.

These three barriers were discussed with over 20 stakeholders from Belgium, allowing us to propose possible solutions. To overcome the lack of awareness about infectious diseases, stakeholders suggested launching national awareness and education campaigns, led by independent organisations. This is a feasible solution, since Belgium has a large expertise in infectious diseases and some survey respondents already plan to try awareness campaigning. There has also been a call from other authors for increased education (20). This would improve the public's knowledge about the

burden of diseases and the need for vaccine development, and therefore harness the public's motivation to take part in a PVT. Judging by the success of campaigns to increase vaccination coverage, we believe that public campaigns and improved education would successfully improve disease awareness (21, 22).

Stakeholders support the renewal of specialist HCP networks. Such networks would allow HCPs to share their experience in clinical trial management, promote vaccinology to peers, increase HCPs' access to certain cohorts and provide a central contact for collaborators. Furthermore, a strong network would allow rapid dissemination of new information and even the sharing of human resources, which we identified as the most popular recruitment strategy. This is a feasible strategy, but would need support to maintain networks.

To reduce the burden of volunteering in a PVT, we considered the possibility of bringing the trial to the subject, instead of asking the subject to come to the trial. Stakeholders suggested using mobile units so that a study visit can be done outside of the clinical trial site, such as at a hospital, day care centre, school, or nursing home. This would eliminate the need for the subject to find transport to the clinical trial site and reduce travel time, therefore reducing the impact on the subject's daily commitments. This strategy has been suggested by other authors (23), although the cost and ability to maintain good clinical and laboratory practice should be carefully considered.

Limitations of the study

The number of vaccine trials in Belgium compared to the large number of non-vaccine studies is relatively small (11), which may explain the small number of survey responses that we received. However, interviews were performed at all sites in Belgium that regularly perform PVTs, which means that we have exhausted the available information from those with direct experience with recruitment.

Conclusion

The present study shows that healthy adults and elderly populations are successfully recruited for PVT in Belgium. The difficult to recruit populations are: paediatric populations, patients, pregnant women and the very elderly. Survey respondents and interviewees use a combination of recruitment strategies, from volunteer databases to advertising and collaboration with other HCPs. The three most significant barriers for participants in this study are: the lack of public knowledge about infectious diseases; the lack of resources of HCPs to take part in PVT; and the burden to potential volunteers to take part in a PVT. Together with stakeholders, we identified new initiatives to overcome these recruitment barriers in Belgium.

Conflict of interest

LH is an employee of GSK and a secondee at the FAMHP. GSK had no influence over the study. The opinion presented in this paper is the one of the author and does not reflect GSK's position. PVD, CV and SM have no conflict of interest.

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